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05 March 2003

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PATENT- OG VAREMÆRKESTYRELSEN

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Process for filming of liquid physiological specimens.

This invention relates to a process, and apparatus for utilising the process, for distribution of liquid physiological specimens on a surface with an array of assays, say a glass slide for subsequent inspection with a microscope. Such distribution is often referred to as "filming" by those working in medical laboratories, and the liquid physiological specimens is often called "sample".

As an example, applying a drop of blood to a slide, where the surface of the slide contains an array of assays, takes place in a DNA-testing process. When the drop of blood is distributed over the surface of the slide, the elements in the blood will react or connect to the assays where they fit, and analysing the slide afterwards will give the result of the DNA-testing.

To reach contact between the elements of the sample and the assays, the elements have to diffuse from the sample to the assays, and obvious the time for this diffusion will increase with the thickness of the sample layer on the surface of the slide. The time for the process will therefore be reduced if the thickness of the layer is reduced, and hence reducing the thickness of the layer is therefore desirable.

By filming the main problem to solve is to equally distribute and re-circulate the sample over the hole of the surface, whereby the sample will be distributed to all

the assays in the array. One way of solving this problem is to place the array of assays flat in a rotating device, whereby the surface is in the same plane as rotational movement. The sample will hereby be forced along the surface, say thrown across the surface, due to the dynamic reaction from the rotation. This dynamic reaction will hence after be refereed to as the centrifugal force, and will be to understand as the act of a particle away from the centre of a rotating movement.

At distribution of a sample by throwing it across the surface of the array of assays, the sample applied to the surface does not distribute equally along the hole of the surface, whereby reproduction of the results is hard to obtain. A single drop of the sample is not likely to distribute along the hole of the surface, and therefore not likely to reach all assays in the array. Furthermore it is likely to be thrown off the surface before reactions have ended. Therefore a number of extra drops are applied to the surface, which will increase the time consumed for each test and increase the used amount of the often expensive sample. Also, each specimens in the sample will be forced along the surface, whereby contact between the specimens and all the assays in the array is hard to obtain, and therefore also influence the reproduction ability of the test.

Another known way of overcoming the problems by the filming process is to force the sample through micro channels, in which the array of assays is contained. This method will reduce the time for the process, but is very sensitive to pollution, the size of the elements in the sample, and the production of the micro channels.

It is an object of this invention to overcome the difficulties with reproduction of test results. It is a further object of this invention to reduce the time consumed with each test, and to reduce the used amount of the sample for each test. A yet further object of the invention is to reduce the sensitivity regarding pollution, surface tension, surface character and the size of the elements in the sample.

The object of this invention is achieved by placing the array of assays in a way where the surface is more or less pointed towards the axis of rotation of the rotating device, whereby the sample will be forced toward the surface under act of the dynamic forces from the rotation. Hereby is achieved that the element in the sample are forced in the direction of the assays, and a drop of the sample will be completely filmed by the dynamic forces.

Preferably the sample is distributed to the hole of the surface, in a layer of equal thickness. Hereby is obtained that all assays in the array is in contact with the sample, and that the elements in the sample will have equal and best conditions for diffusion to the assays. Even small amounts of sample will due to dynamic forces still be in contact with all the assays in the array.

It is an advance that the distribution of the sample is controlled by adjusting the position of the surface, relative to the axis of rotating. Hereby is it possible to control the direction of the distribution, and the rate at which the sample distribute over the surface.

It is an advance that the array of assays itself further rotates around another axis than that of the rotating

device, whereby the elements in the sample will be distributed to all, or nearly all, assays in the array.

Preferably the sample is re-circulated over the surface, hereby achieving that each element of the sample will have more than just one opportunity to reach contact with an assay which fit or matches the elements.

It is specific preferable that the surface, to which the sample is applied, is formed as a hollow in a material part, where the hollow forms a closed container when the material part is covered with a lid, and where the sample is applied to the surface before the lid covers the hollow. The sample is hereby contained in a closed container, and can be re-circulated over the surface without having any disturbing and/or damaging contact with the surroundings.

This closed container is also an advantage when dealing with infectious or dangerous bio-sample: Since the sample does not get in contact with the surrounding air.

The invention will now be described in details with references to the drawings, showing:

- Fig. 1: Working principle and a principal embodiment of the invention.
- Fig. 2: Principle of a part of an apparatus in accordance with the invention.
- Fig. 3: Detailed part of an apparatus in accordance with the invention.
- Fig. 4: An embodiment of an array of assays, placed in a hollow.
- Fig. 5: Device containing two arrays of assays, placed in a hollow.

- Fig. 6: Rotating array of assays in accordance with the invention.
- Fig. 7: Functional view describing the process of re-circulation in accordance with fig. 6.
- Fig. 8: An embodiment of a rotating device.
- Fig. 9: An embodiment of a rotating device

On figure 1A is shown a sectional view of a slide 1, having a surface 2 with an array of assays 3. Such slides are widely used in laboratories, e.g. for microscope analyse of blood specimens. The slide of figure 1A has a frame part 4 along tree of the sides, which will be understood from the sectional view in figure 1B. The forth side 5 is formed and works as a drain part, from where the specimens can flow away from the surface 2.

The slide 1 is placed in a rotating device 9 of figure 2, the device containing multiple sections 13. Figure 3 shows one of the sections 13 in a sectional view, and with the slide 1 placed in the holder 14. As the rotating device is rotating, centrifugal forces will act from the centre of rotation, and at right angle, towards the circumference 12 of the rotating device 9. The plunger part 11 of figure 2 will be forced towards the part 16 of figure 3, due to the dynamic forces or an automatically controlled movement, and liquid sample contained behind part 16 will under this pressure be dosed as drops by a capillary part 17, and led through the pipe 18 to the slide 1. The mouth of the pipe ends at the end of the slide where the holder is placed, and in some distance from the slide. The slide itself is placed in an upright position along the circumference 12 of the rotating device 9, whereby the centrifugal force will act substantially parallel to a normal axis of the surface of the slide. The surface of the slide 1 is

therefore substantially parallel to the rotating axis of the rotating device.

The drop 6 in figure 1 A and 1B is a drop which just have left the pipe 18, and as the drop hits the surface of the slide, it will be distributed along the surface due to the centrifugal force. This is indicated by arrows at figure 1C to 1F, and the frame 4 on the tree sides of the slide 1 will force the distribution towards the drain part 5 of the slide 1, from where drops 7 will be thrown of the slide. The centrifugal force has now distributed a thin layer of the sample over the hole of the surface, and every assay 3 in the array has reach contact with the sample.

The velocity with which the sample is distributed towards the drain part 5 can be controlled by controlling the angular position of the slide, and by controlling the rotational speed of the rotating device. As the distribution along the surface is controllable, only a very little amount of sample liquid is needed for each slide. As a consequence of the dynamic forces, surface tensions will only have limited effect.

In some test application it is of importance that the used amount of sample liquid is reduced to a minimum, and that the applied sample liquid is kept on the surface of the slide, and not thrown away over a drain part as previously described. This is known as re-circulation of the sample along the surface. In figure 4 is shown a structure 19, placed in a hollow, which has a surface 2 with an array of assays 3, and supplied with a number of small pockets 20 places along the circumference of the structure. This structure is formed as a hollow 19 in a material part 21, shown at figure 5, with a lid 22 on top of it. When the

lid is placed on top of the material part 21, each of the two hollows 19 and 19a forms a small test volume, and the assembled material part with lid forms a slide 26.

In figure 6 is shown the slide 26 placed in a rotating device with an axis of rotation 10, the rotation indicated by arrow 24. The slide 26 is placed at a centre line 23 that is placed at an angle Y relative to the rotating axis 10, and in a distance X from the rotating axis 10, whereby the centrifugal force will act on the surface as previously described with a normal portion. In addition, the dynamic forces will act on the surface with a tangential portion, whereby the sample is forces across the surface. The slide 26 is rotated around the centre line 23, indicated by arrow 25. The effect of this additional rotation 25 will be described with reference to figure 7.

Figure 7A shows a drop of a liquid sample applied to the test volume in the container, and the lid is then placed on top of the container. The slide 26 is then placed in the rotating device, whereby the centrifugal force will act on the surface and filming the sample on the array of assays. Some of the sample will be distributed into the small pockets, and as the slide 26 rotates around an axis, the liquid sample will flow from one pocket to the array of assays, and along the circumference to the next pockets, indicated at figure 7B. The shape of the pockets will however distribute liquid sample over the hole of the array of assays, as the slide 26 is rotated, indicated at figure 7C to 7E. Each pocket then acts as a collecting area, from where liquid sample once again is distributed to the array of assays, and re-circulation occurs. When exiting the pockets, the exit channel and exit hole are

formed in a way that prevents the sample from flowing only along the circumference.

Re-circulation as described in figure 7 is basically the same effect as that, known from a washing machine. The sample is again and again washed across the array of assays, whereby reproduction of the testing is to be obtained through counting the number of rotations, rotational speed, etc.

On figure 8 is shown another embodiment of a rotating slide in a rotating device. The slide 28 is now formed as a cylinder part, which rotates around its own axis 27. The axis 27 is more or less parallel to the rotation axis 10 of the rotating device, and the centrifugal force will thus act on the surface of the slide 28. The array of assays is placed on the inner surface of the slide 28, and the slide has on top and on bottom a frame part 4, extending from the inner surface of the cylinder and towards the axis of rotation 27. As a drop of the liquid sample is applied inside the slide 28, it will be distributed as a column along the inner surface, and the column will be placed where the distance from axis of rotation 10 is largest. As the slide is rotated around axis 27, the column will wash the hole of the inner surface, and hereby re-circulation will occur.

On figure 9 is shown a third embodiment of a rotating slide in a rotating device. Here the slide is formed as a cone part 30, which rotates around its own axis 29. The axis 29 is placed in an angle relative to the rotation axis 10 of the rotating device, whereby a part of the inner surface of the cone shaped slide will be more or less parallel to the rotation axis 10 of the rotating device, and the centrifugal force will thus act on this

part of the inner surface of the cone shaped slide 30. A column of liquid sample 31 will, due to the centrifugal force, be formed on the inner part of the cone shaped slide, which is more or less parallel to the axis of rotation 10. As the cone shaped slide is rotated around its own axis 29, liquid sample will wash the hole of the inner surface, and hereby re-circulation will occur.

The invention can, as mentioned in the beginning of the application, be utilised in laboratories for DNA-testing. However this application does not in any way limit the invention. A slide can contain similar assays for reaction with specific elements or different assays for reaction with a group of elements. The invented process can be utilised for distribution of a sample over any surface of a slide, and the application will then depend on the slide used in the process.

Thus, a portable apparatus for testing purpose on locations is a possibility. This could be an apparatus for testing for diseases when consulting a doctor, or an apparatus for testing for cultures of bacteria in watercourse. Only the slide used in the process defines the application for a given apparatus.

Claims

1. Process for centrifugal distribution of liquid physiological specimens over a surface with an array of assays, wherein said array of assays is placed in a rotating device and said liquid physiological specimens is distributed to said surface due to the reaction from the dynamic forces from the rotation, characterised in that said surface (2) is pointed towards the axis of rotation (10), whereby the liquid physiological specimens will be forced toward said surface (2) under act of the dynamic forces from the rotation.

2. Process in accordance with claim 1, characterised in that said liquid physiological specimens will be distributed to the hole of said surface (2), in a layer of equal thickness.

3. Process in accordance with claim 2, characterised in that the distribution of said liquid physiological specimens is controlled by adjusting the position of said surface (2), relative to said axis of rotating (10).

4. Process in accordance with claim 1, characterised in that said array of assays is rotating around an other axis (23, 27, 29) than that of the rotating device (10).

5. Process in accordance with claim 4, characterised in that said liquid physiological specimens is re-

circulated over said surface (2).

6. Process in accordance with claim 5, characterised in that said surface (2), to which said liquid physiological specimens is applied, is formed as a hollow (19) in a material part (21), said hollow (19) forming a closed container when the material part (21) is covered with a lid (22), and said liquid physiological specimens being applied to said surface (2) before said lid (22) covers said hollow (19).

7. Apparatus for centrifugal distribution of liquid physiological specimens characterised in that it utilises a process in accordance with claim 1.

Abstract

This invention disclose an improved process of distribute a liquid physiological specimens over a surface, i.e. the filming process in a laboratory under which a liquid sample is distributed over a specimen-display surface like a conventional laboratory slide. The invention relates to the utilisation of the centrifugal force in a rotating device. By placing the surface, that is to be filmed by the sample, in a way where it is pointed towards the axis of rotation, the act of the centrifugal force will distribute the sample over the hole of the surface.

FIG 1A

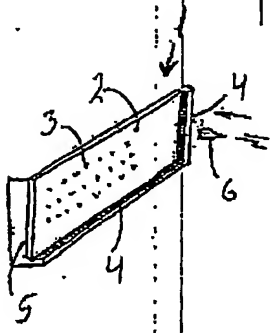


FIG 1B

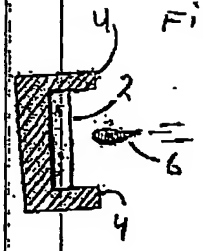


FIG 1C

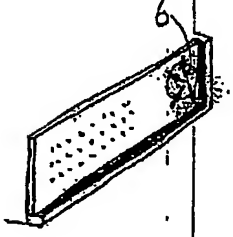


FIG 1D

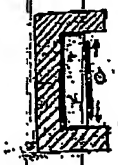


FIG 1E

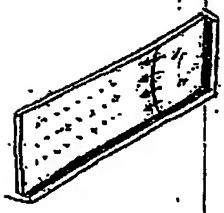


FIG 1G

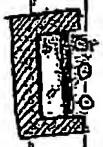


FIG 1F

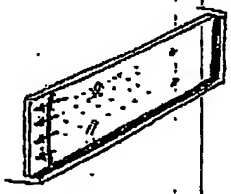


FIG 1H

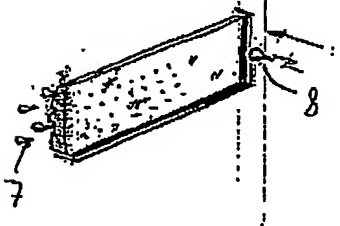


FIG 2

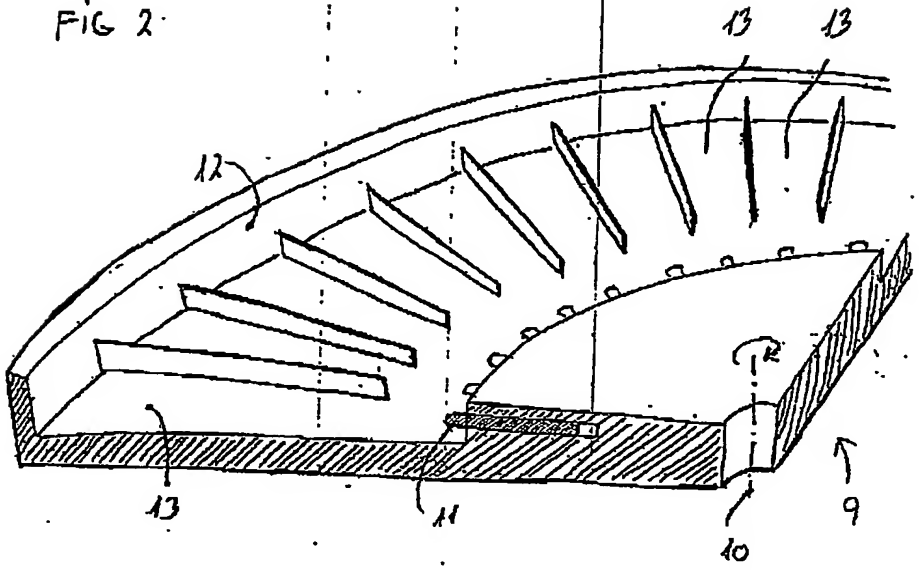


FIG 3

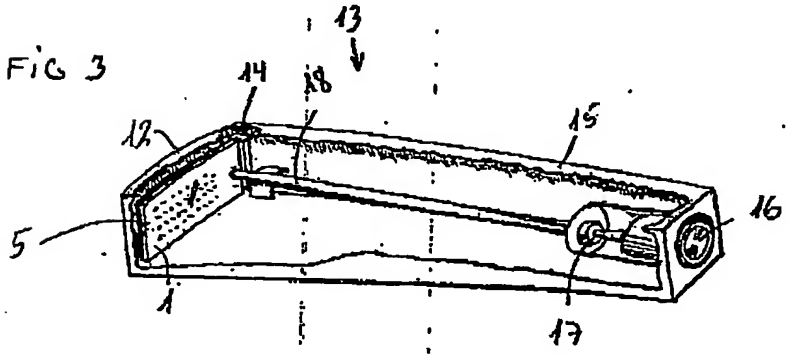


FIG 4

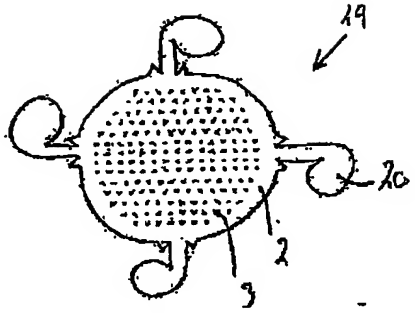
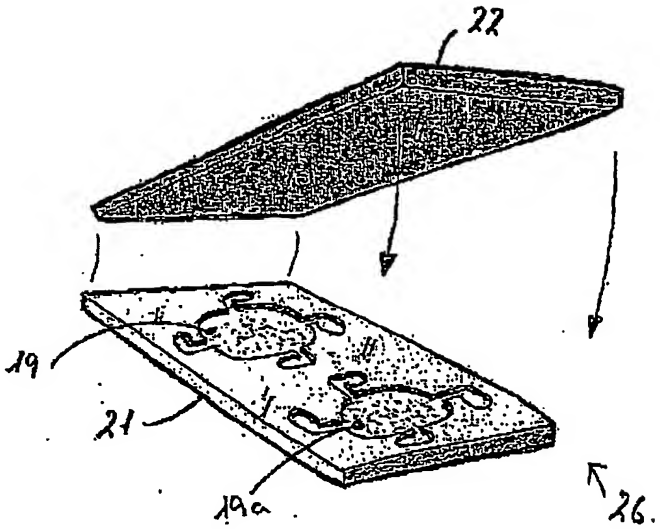


FIG 5



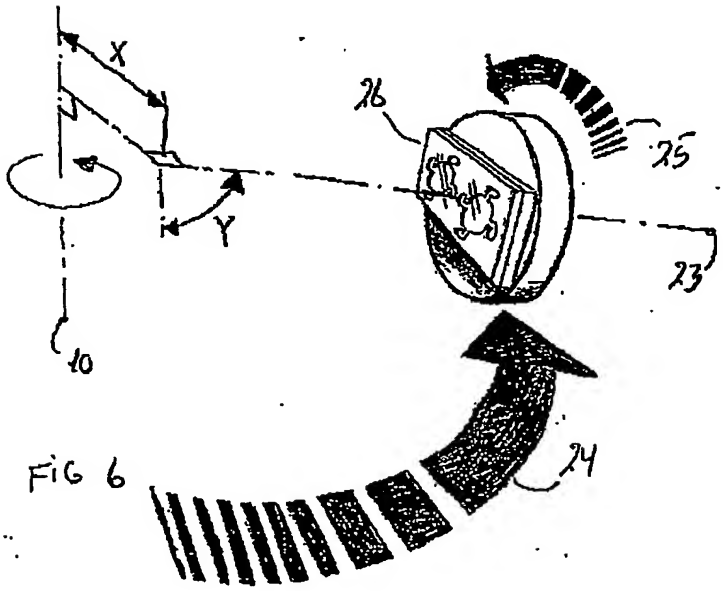


FIG 6

FIG 7A

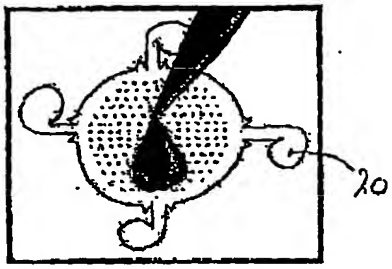


FIG 7B

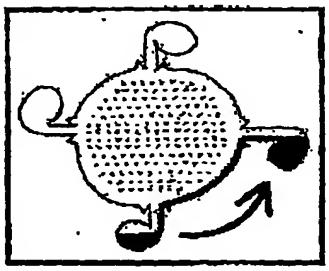


FIG 7C

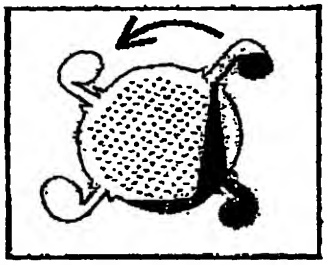


FIG 7D

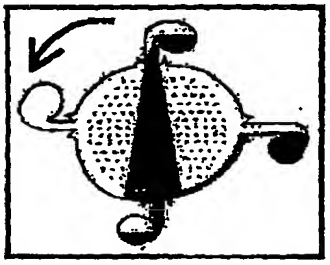


FIG 7E

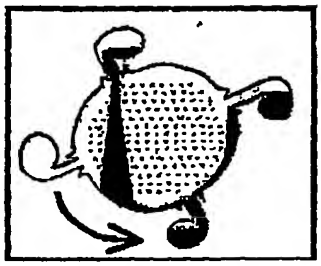


FIG 8

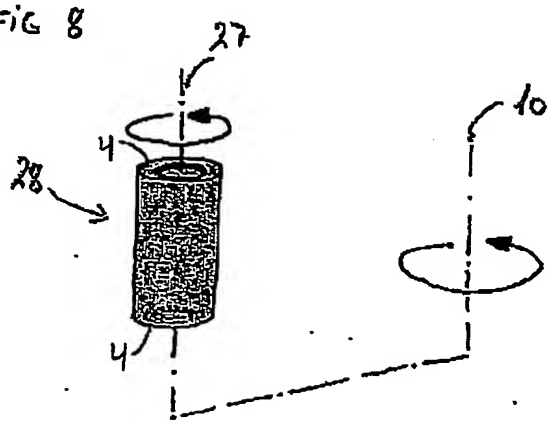


FIG 9